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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/016,149	11/01/2001	C. Frank Bennett	RTS-0325	4677

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Jane Massey Licata
Licata & Tyrrell, P.C.
66 East Main Street
Marlton, NJ 08053

EXAMINER	
SCHULTZ, JAMES	
ART UNIT	**PAPER NUMBER**
1635	4

DATE MAILED: 06/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Fig 6

Office Action Summary	Application No.	Applicant(s)	
	10/016,149	BENNETT ET AL.	
	Examiner	Art Unit	
	J. Douglas Schultz	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 February 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 4-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 4-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3* .
4) ☒ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's preliminary amendment filed February 25, 2003 has been fully entered.

Claim Rejections - 35 USC § 112

Claims 15-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for antisense-mediated inhibition of phospholipase A2 group V expression *in vitro*, does not reasonably provide enablement for antisense-mediated inhibition of phospholipase A2 group V expression *in vivo*, or for methods of treating diseases associated with its expression *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The above invention is drawn to methods of inhibiting the expression of phospholipase A2 group V in cells or tissues comprising contacting said cells or tissues with antisense compositions that inhibit the expression of phospholipase A2 group V. The claims of the above invention are also drawn to methods of treating an animal having a condition associated with phospholipase A2 group V, wherein said compositions are administered to animals such that expression of phospholipase A2 group V is inhibited, wherein said condition may be a hyperproliferative disorder including an autoimmune or inflammatory disorder. The language of said claims encompasses both *in vivo* and *in vitro* activity. The specification teaches a method of

using the claimed compositions to inhibit the expression of phospholipase A2 group V in cells *in vitro*.

The specification as filed does not provide any guidance or examples that would enable a skilled artisan to use the disclosed compounds or methods of using said compounds in *in vivo* environments. Additionally, a person skilled in the art would recognize that predicting the efficacy of an antisense compound *in vivo* based solely on its performance *in vitro* is highly problematic. Thus, although the specification prophetically considers and discloses general methodologies of using the claimed constructs *in vivo* or in methods of inhibition or treatment, such a disclosure would not be considered enabling since the state of antisense-mediated gene inhibition is highly unpredictable. The factors listed below have been considered in the analysis of enablement:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The following references are cited herein to illustrate the state of the art of antisense treatment. Although some of the cited references were published beyond the filing date of the instant application, they are presented here to demonstrate that even today, critical issues related to the practice of nucleic acid therapies remain unresolved.

A recent (2002) article by Braasch et al. emphasizes that major obstacles persist in the art: "gene inhibition by antisense oligomers has not proven to be a robust or generally reliable

technology. Many researchers are skeptical about the approach, and it has been suggested that many published studies are at least partially unreliable" (Pg. 4503, para. 1 and 2). Braasch et al. goes on to identify factors that contribute to the unpredictable efficacy of antisense compounds *in vivo*: poor antisense oligonucleotide access to sites within the mRNA to be targeted, difficulties with delivery to and uptake by cells of the antisense oligos, toxicity and immunological problems caused by antisense oligos, and artifacts created by unpredictable binding of antisense compounds to systemic and cellular proteins.

Regarding the difficulties of predicting whether antisense oligonucleotides can access sites within their target mRNA, Braasch et al. explains, "it has been difficult to identify oligonucleotides that act as potent inhibitors of gene expression, primarily due to difficulties in predicting the secondary structures of RNA (Pg. 4503, para. 1 and 2). Branch adds that "internal structures of target RNAs and their associations with cellular proteins create physical barriers, which render most potential binding sites inaccessible to antisense molecules" (Page 45, third column). Additionally, in a review of the potential use of antisense oligos as therapeutic agents, Gewirtz et al. teach that the inhibitory activity of an oligo depends unpredictably on the sequence and structure of the nucleic acid target site and the ability of the oligo to reach its target. (Page 3161, second and third columns).

The uptake of oligonucleotides by cells has been addressed by Agrawal, who states, "[o]ligonucleotides must be taken up by cells in order to be effective....several reports have shown that efficient uptake of oligonucleotides occurs in a variety of cell lines, including primary cells whereas other reports indicate negligible cellular uptake of oligonucleotides. Cellular uptake of oligonucleotides is complex process; it depends on many factors, including the

cell type, the stage of the cell cycle, the concentration of serum. It is therefore, difficult to generalize that all oligonucleotides are taken up in all cells with the same efficiency" (Page 378). "[M]icroinjection or using lipid carriers to supply an oligonucleotide in cell culture increases the potency of the oligonucleotide in cell culture, but it is not clear how relevant this approach is for *in vivo* situations." (Page 379).

Braasch et al. discuss the non-specific toxicity effects of *in vivo* antisense administration; "even when active oligomers are discovered, the difference in oligonucleotide dose required to inhibit expression is often not much different than doses that lead to nonselective toxicity and cell death...oligonucleotides can bind to proteins and produce artifactual phenotypes that obscure effects due to the intended antisense mechanism" (Pg. 4503, para. 1 and 2). Branch affirms that "non-antisense effects are not currently predictable, rules for rational design cannot be applied to the production of non-antisense drugs, These effects must be explored on a case by case basis" (Page 50), while Tamm et al. states that "[i]mmune stimulation is widely recognized as an undesirable side-effect...the immunostimulatory activity of a phosphorothioate-modified oligonucleotide is largely unpredictable and has to be ascertained experimentally" (page 493, right column).

Further, Branch reasons that "the value of a potential antisense drug can only be judged after its intended clinical use is known, and quantitative information about its dose-response curves and therapeutic index is available" (Page 46, second column). Tamm et al. concludes by stating that until "the therapeutic activity of an antisense oligonucleotide is defined by the antisense sequence, and thus is to some extent predictable...antisense will not be better than other drug development strategies, most of which depend on an empirical approach."

The specification of the instant application fails to provide adequate guidance for one of skill in the art to overcome the unpredictability and challenges of applying results from *in vitro* experiments to the *in vivo* treatment of disease, or *in vivo* methods of inhibition, as exemplified in the references above.

Furthermore, one skilled in the art would not accept on its face the examples given in the specification of the inhibition of phospholipase A2 group V expression *in vitro* as being correlative or representative of the successful *in vivo* use of antisense compounds or treatment of any and/or all conditions or diseases suspected of being associated with phospholipase A2 group V expression. This is particularly true in view of the lack of guidance in the specification and known unpredictability associated with the efficacy of antisense in treating or preventing any conditions or disease suspected of being associated with a particular target gene *in vivo*. The specification as filed fails to provide any particular guidance which resolves the known unpredictability in the art associated with appropriate *in vivo* delivery and treatment effects provided by antisense administered, and specifically regarding the instant compositions and methods claimed.

Said claims are drawn very broadly to methods of treating cells *in vivo* or to treating or preventing any condition or disease suspected of being associated with phospholipase A2 group V expression in humans. Since the specification fails to provide any guidance for the successful treatment or prevention of such a broad range of diseases, and since resolution of the various complications in regards to targeting a particular gene in an organism is highly unpredictable, one of skill in the art would have been unable to practice the invention without engaging in undue trial and error experimentation. In order to practice the invention using the specification

and the state of the prior art as outlined above, the quantity of experimentation required to practice the invention as claimed *in vivo* would require the *de novo* determination of formulations with acceptable toxicity and immunogenicity that are successfully delivered to target sites in appropriate cells and /or tissues. In the absence of any real guidance from the specification, the amount of experimentation would be undue, and one would have been unable to practice the invention over the scope claimed.

Claim Rejections - 35 USC § 102/103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 and 103 that form the basis for the rejections under these sections made in this Office action:

> A person shall be entitled to a patent unless –
>
> 102(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> 102(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> 102 (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.
>
> 103(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2 and 11 are rejected under 35 U.S.C. 102(b) and 103(a) as being anticipated and/or obvious by Tischfield et al., *supra*.

The claims of the above invention are drawn to antisense compounds 8 to 50 nucleotides in length that specifically hybridize with and inhibit the expression of phospholipase A2 group V (applicants' instant SEQ ID NO: 3).

SEQ ID NOS: 15, 16, and 18 of Tischfield et al. possess 100%, 100% and 96.3% identity, respectively, with residues 294-315, 522-543, and 526-552, respectively, of the instant target of SEQ ID NO: 3.

Although this reference does not specifically teach the function of inhibiting applicants' instant SEQ ID NO: 3 as claimed in the present application, the above-listed compound meets all the structural limitations as set forth in the instant claims. Because the sequence is substantially identical to applicant's claimed compounds, in the absence of evidence to the contrary said compound is thus considered to possess the functional limitation of specifically hybridizing with and inhibiting the expression of applicants' instant SEQ ID NO: 3. Support for this conclusion is drawn from MPEP 2112;

> Where applicant claims a composition in terms of a function, property or characteristic and the composition of the prior art is the same as that of the claim **but the function is not explicitly disclosed by the reference, the examiner may make a rejection under both 35 U.S.C. 102 and 103, expressed as a 102/103 rejection**. "There is nothing inconsistent in concurrent rejections for obviousness under 35 U.S.C. 103 and for anticipation under 35 U.S.C. 102." *In re Best*, 562 F.2d 1252, 1255 n.4, 195 USPQ 430, 433 n.4 (CCPA 1977). This same rationale should also apply to product, apparatus, and process claims claimed in terms of function, property or characteristic. Therefore, a 35 U.S.C. 102/103 rejection is appropriate for these types of claims as well as for composition claims. *Emphasis supplied.*

In rejecting the claims of the above under 35 U.S.C. 102 and 103, a prima facie case has been established by the examiner whereby the burden of proof in showing that the claimed compounds are not anticipated by the compound(s) of the prior art as stated lies with the applicant, as per MPEP 2112.01:

> Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or

obviousness has been established. In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not. *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the prima facie case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. *In re Best*, 562 F.2d at 1255, 195 USPQ at 433.

Claims 1, 2 and 11 are rejected under 35 U.S.C. 102(a) and 103(a) as being anticipated and/or obvious by Chen et al., (PubMed accession number AB067851, Genomics, 2001. 74(1) 55-70).

The claims are drawn to the invention as described above

The reverse primer of human STS sts-stSG1697 of Chen et al. possesses 100% identity with residues 966-989 of the instant target of SEQ ID NO: 3. This reference is considered to anticipate or render obvious claims 1, 2, and 11 for the same reasons as discussed above.

Claims 1, 2 and 11-14 are rejected under 35 U.S.C. 102(e) and 103(a) as being anticipated and/or obvious by Shimkets et al., (WO 01/47944 A2).

The claims are drawn to the invention as described above, and are additionally drawn to the instantly claimed compounds comprising pharmaceutical diluents and dispersion systems.

SEQ ID NO: 5308 of Shimkets et al. possesses 100% identity with residues 918-967 of the instant target of SEQ ID NO: 3. Furthermore, Shimkets et al. teaches that this sequence may be administered as part of a pharmaceutical composition comprising a carrier or dispersion system that meets the limitations of claims 12-14 (for example see page 38). This reference is over 4,400 pages, the vast majority of which consists of a sequence listing; therefore the

complete text of the specification, the relevant page containing the instantly contemplated SEQ ID NO: 5308, and the claims have been included. Should applicant require the remaining sequence listing of over 4,350 pages, please contact the examiner at the phone number or fax given below, and a copy will be provided.

This reference is considered to anticipate or render obvious claims 1, 2, and 11-14 for the same reasons as discussed above.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2 and 4-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tischfield et al., in view of Balboa et al. (J. Biol. Chem, 1996. 271(50) 32381-32384), Taylor et al., and Baracchini et al. (U.S. Patent Number 5,801,154).

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The invention of the above claims is drawn to antisense compounds that target phospholipase A2 group V (applicants' instant SEQ ID NO: 3), or its active sites or said compounds comprising internucleoside, sugar, nucleobase, and 2' modifications, chimeras, or compositions comprising said compounds and pharmaceutically acceptable diluents thereof.

Tischfield et al. teach the sequence encoding phospholipase A2 group V (applicants' instant SEQ ID NO: 3), and also teach antisense inhibition of SEQ ID NO: 3. Tischfield et al. does not teach oligonucleotides 8 to 50 nucleobases that comprise internucleoside, sugar, nucleobase, chimeras, and 2' modifications, or compositions comprising said compounds and pharmaceutically acceptable diluents thereof. Applicants further claim a method of using said compounds.

Balboa et al. teach an antisense compound 21 nucleotides in length, wherein said compound is in a composition comprising a pharmaceutical diluent and a method of using said compound to target inhibit the expression of murine phospholipase A2 group V, which is homologous with applicant's instant claimed target of SEQ ID NO: 3.

Taylor et al. teach the inhibition of expression of any protein using a known cDNA sequence to generate antisense oligos that target that and inhibit the expression of that protein, and also teach that with software analysis and high affinity oligos, one needs to screen only 3-6 oligos to find one that inhibits its target 66-95% (p. 565).

Baracchini et al. teaches modifications of antisense compounds comprising sugar, nucleobase, 2' modifications, chimeras, and compositions comprising said compounds and

pharmaceutically acceptable diluents thereof. Baracchini et al. also teach targeting specific regions of a gene including the 5'-untranslated, start codon, coding, stop codon, or 3'-untranslated regions, and demonstrate the methods necessary to achieve gene inhibition.

It would have been obvious to one of ordinary skill in the art to make antisense sequences to target the cDNA sequence of phospholipase A2 group V as taught by Tischfield et al. for inhibition of phospholipase A2 group V expression, and further, it would have been obvious to one of ordinary skill in the art to incorporate modifications as taught by Baracchini et al. into said antisense compounds. One would have been motivated to create such compounds because Tischfield et al. expressly teach antisense inhibition of applicants' instant phospholipase A2 group V target of SEQ ID NO: 3, and further, because Balboa et al. expressly teach antisense-mediated-inhibition of the homologous murine homologue *in vitro* using antisense oligonucleotides 8 to 50 nucleobases in length in a method of interfering with a cellular signaling pathway related to inflammation. One would have been motivated to modify said antisense compounds as taught by Baracchini et al., because Baracchini et al. teach that such modifications increase an antisense compound's cellular uptake, target affinity and resistance to degradation. Finally, one would have a reasonable expectation of success given that Taylor teaches that with software analysis and high affinity oligos, one needs to screen only 3-6 oligos to find one that inhibits its target 66-95% *in vitro*, and since Baracchini et al. teach making modified antisense compounds targeted to distinct regions of a target gene, the steps of which are routine to one of ordinary skill in the art.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Douglas Schultz whose telephone number is 703-308-9355. The examiner can normally be reached on 8:00-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 703-308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

James Douglas Schultz, PhD
June 1, 2003

KAREN LACOURCIERE
PATENT EXAMINER